Table 2-9 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : in-the-hand observations (Week 3)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Ease of removal from cage									
Easy		12	6	6	12	11	6	6	12
Some resistance/avoidance		0	0	0	0	1	0	0	0
Fur condition									
Normal		12	6	6	12	12	6	6	12
Skin									
Normal		12	6	6	12	12	6	6	12
Secretions-Eye, Nose									
Absent		12	6	6	12	12	6	6	12
Exophthalmos									
Absent		12	6	6	12	12	6	6	12
Palpebral closure									
Normal		12	6	6	12	12	6	6	12
Mucosal membranes									
Normal		12	6	6	12	12	6	6	12
Lacrimation									
Normal		12	6	6	12	12	6	6	12
Piloerection									
Absent		12	6	6	12	12	6	6	12
Pupil size									
Normal		12	6	6	12	12	6	6	12
Salivation									
None		12	6	6	12	12	6	6	12
Abnormal respiration									
Absent		12	6	6	12	12	6	6	12
Reactivity to handling									
Easy		12	6	6	12	12	6	6	12

No significant difference in any treated groups from control group.

Table 2-10 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : in-the-hand observations (Week 4)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Ease of removal from cage									
Easy		12	6	6	12	12	6	6	12
Fur condition									
Normal		12	6	6	12	12	6	6	12
Skin									
Normal		12	6	6	12	12	6	6	12
Secretions-Eye, Nose									
Absent		12	6	6	12	12	6	6	12
Exophthalmos									
Absent		12	6	6	12	12	6	6	12
Palpebral closure									
Normal		12	6	6	12	12	6	6	12
Mucosal membranes									
Normal		12	6	6	12	12	6	6	12
Lacrimation									
Normal		12	6	6	12	12	6	6	12
Piloerection									
Absent		12	6	6	12	12	6	6	12
Pupil size									
Normal		12	6	6	12	12	6	6	12
Salivation									
None		12	6	6	12	12	6	6	12
Abnormal respiration									
Absent		12	6	6	12	12	6	6	12
Reactivity to handling									
Easy		12	6	6	12	12	6	6	12

No significant difference in any treated groups from control group.

Table 2-11 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : in-the-hand observations (Week 1 of recovery)

	Sex	Male		Female	
	Dose (mg/kg)	0	1000	0	1000
Parameter	No. of animals	6	6	6	6
Ease of removal from cage					
Easy		6	6	6	6
Fur condition					
Normal		6	6	6	6
Skin					
Normal		6	6	6	6
Secretions-Eye, Nose					
Absent		6	6	6	6
Exophthalmos					
Absent		6	6	6	6
Palpebral closure					
Normal		6	6	6	6
Mucosal membranes					
Normal		6	6	6	6
Lacrimation					
Normal		6	6	6	6
Piloerection					
Absent		6	6	6	6
Pupil size					
Normal		6	6	6	6
Salivation					
None		6	6	6	6
Abnormal respiration					
Absent		6	6	6	6
Reactivity to handling					
Easy		6	6	5	6
Slightly awkward		0	0	1	0

No significant difference between treated group and control group.

Table 2-12 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : in-the-hand observations (Week 2 of recovery)

	Sex	Male		Female	
	Dose (mg/kg)	0	1000	0	1000
Parameter	No. of animals	6	6	6	6
Ease of removal from cage					
Easy		6	6	6	6
Fur condition					
Normal		6	6	6	6
Skin					
Normal		6	6	6	6
Secretions-Eye, Nose					
Absent		6	6	6	6
Exophthalmos					
Absent		6	6	6	6
Palpebral closure					
Normal		6	6	6	6
Mucosal membranes					
Normal		6	6	6	6
Lacrimation					
Normal		6	6	6	6
Piloerection					
Absent		6	6	6	6
Pupil size					
Normal		6	6	6	6
Salivation					
None		6	6	6	6
Abnormal respiration					
Absent		6	6	6	6
Reactivity to handling					
Easy		6	6	6	6

No significant difference between treated group and control group.

Table 2-13 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : open field observation (Week 1)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Arousal									
Normal		12	6	6	12	12	6	6	12
Convulsion									
None		12	6	6	12	12	6	6	12
Abnormal behavior									
None		12	6	6	12	12	6	6	12
Stereotypy									
None		12	6	6	12	12	6	6	12
Gait									
Normal		12	6	6	12	12	6	6	12
Posture									
Normal		12	6	6	12	12	6	6	12
Grooming									
None		12	6	6	12	12	6	6	12
Rearing count (Mean±S.D.)		5± 1	4± 2	5± 2	5± 3	8± 3	9± 4	6± 1	6± 2
Defecation count (Mean±S.D.)		0± 1	1± 1	0± 1	1± 1	0± 0	0± 0	0± 0	0± 0
Urination									
None		11	4	6	9	12	6	6	11
Small amount		1	1	0	3	0	0	0	1
Moderate amount		0	1	0	0	0	0	0	0

No significant difference in any treated groups from control group.

Table 2-14 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : open field observation (Week 2)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Arousal									
Normal		12	6	6	12	12	6	6	12
Convulsion									
None		12	6	6	12	12	6	6	12
Abnormal behavior									
None		12	6	6	12	12	6	6	12
Stereotypy									
None		12	6	6	12	12	6	6	12
Gait									
No/minimal location		0	0	0	0	0	0	0	1
Normal		12	6	6	12	12	6	6	11
Posture									
Normal		12	6	6	12	12	6	6	12
Grooming									
None		12	6	6	12	12	6	6	12
Rearing count (Mean±S.D.)		4± 2	3± 1	4± 3	5± 3	8± 2	8± 4	6± 2	7± 4
Defecation count (Mean±S.D.)		0± 1	0± 1	1± 1	1± 1	0± 0	0± 0	0± 0	0± 0
Urination									
None		10	6	5	9	12	6	6	11
Small amount		2	0	1	3	0	0	0	1

No significant difference in any treated groups from control group.

Table 2-15 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : open field observation (Week 3)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Arousal									
Normal		12	6	6	12	12	6	6	12
Convulsion									
None		12	6	6	12	12	6	6	12
Abnormal behavior							a)		
None		12	6	6	12	12	5	6	12
Minor		0	0	0	0	0	1	0	0
Stereotypy									
None		12	6	6	12	12	6	6	12
Gait									
No/minimal location		1	1	0	1	0	0	0	0
Normal		11	5	6	11	12	6	6	12
Posture									
Normal		12	6	6	12	12	6	6	12
Grooming									
None		12	6	6	12	12	6	6	12
Rearing count (Mean±S.D.)		4± 2	2± 1	6± 3	5± 3	9± 1	9± 4	7± 3	7± 3
Defecation count (Mean±S.D.)		0± 1	0± 0	0± 0	0± 1	0± 0	0± 0	0± 0	0± 0
Urination									
None		9	4	4	10	11	6	6	12
Small amount		2	2	1	0	1	0	0	0
Moderate amount		1	0	1	2	0	0	0	0

a): Running
No significant difference in any treated groups from control group.

Table 2-16 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : open field observation (Week 4)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Arousal									
Normal		12	6	6	12	12	6	6	12
Convulsion									
None		12	6	6	12	12	6	6	12
Abnormal behavior						a)			
None		12	6	6	12	11	6	6	12
Minor		0	0	0	0	1	0	0	0
Stereotypy									
None		12	6	6	12	12	6	6	12
Gait									
No/minimal location		0	1	0	0	0	0	0	1
Normal		12	5	6	12	12	6	6	11
Posture									
Normal		12	6	6	12	12	6	6	12
Grooming									
None		12	6	6	12	12	6	6	12
Rearing count (Mean±S.D.)		5± 3	3± 2	5± 2	5± 2	9± 2	8± 3	8± 2	7± 4
Defecation count (Mean±S.D.)		0± 0	0± 1	0± 0	0± 1	0± 0	0± 0	0± 0	0± 0
Urination									
None		9	4	6	10	12	6	6	12
Small amount		2	2	0	2	0	0	0	0
Moderate amount		1	0	0	0	0	0	0	0

a): Running
No significant difference in any treated groups from control group.

Table 2-17 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : open field observation (Week 1 of recovery)

	Sex	Male		Female	
	Dose (mg/kg)	0	1000	0	1000
Parameter	No. of animals	6	6	6	6
Arousal					
Normal		6	6	6	6
Convulsion					
None		6	6	6	6
Abnormal behavior					
None		6	6	6	6
Stereotypy					
None		6	6	6	6
Gait					
No/minimal location		1	0	0	0
Normal		5	6	6	6
Posture					
Normal		6	6	6	6
Grooming					
None		6	6	6	6
Rearing count (Mean±S.D.)		5± 3	5± 1	8± 2	6± 2*T
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		6	5	5	6
Small amount		0	1	1	0

* : $p<0.05$ (Significant difference from control group)
T : Student's t-test

Table 2-18 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Detailed clinical signs : open field observation (Week 2 of recovery)

Parameter	Sex	Male		Female	
	Dose (mg/kg)	0	1000	0	1000
	No. of animals	6	6	6	6
Arousal					
Normal		6	6	6	6
Convulsion					
None		6	6	6	6
Abnormal behavior					
None		6	6	6	6
Stereotypy					
None		6	6	6	6
Gait					
No/minimal location		1	0	0	0
Normal		5	6	6	6
Posture					
Normal		6	6	6	6
Grooming					
None		6	6	6	6
Rearing count (Mean±S.D.)		5± 3	4± 2	10± 2	9± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		5	6	6	6
Small amount		1	0	0	0

No significant difference between treated group and control group.

Table 2-19 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Manipulative test (Week 4)

	Sex	Male				Female			
	Dose (mg/kg)	0	100	300	1000	0	100	300	1000
Parameter	No. of animals	12	6	6	12	12	6	6	12
Auditory response									
Weak		0	0	0	2	0	0	2	1
Normal		12	6	6	10	12	6	4	11
Approach response									
Normal		12	6	6	12	12	6	6	12
Touch response									
Normal		12	6	6	12	12	6	6	12
Tail pinch response									
Normal		11	6	6	12	10	6	6	12
Exaggerate		1	0	0	0	2	0	0	0
Pupillary reflex									
Pass, both		12	6	6	12	12	6	6	12
Aerial righting reflex (Total score: Mean±S.D.)		0± 0	0± 0	0± 0	0± 0	0± 0	0± 0	0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		78±11	68±13	72±18	91±10*D	59±19	47±15	63±19	79± 5*DT

* : $p<0.05$ (Significant difference from control group)
D : Dunnett's test
DT : Dunnett-type rank test

Table 2-20 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Manipulative test (Week 2 of recovery)

	Sex	Male		Female	
	Dose (mg/kg)	0	1000	0	1000
Parameter	No. of animals	6	6	6	6
Auditory response Normal		6	6	6	6
Approach response Normal		6	6	6	6
Touch response Normal		6	6	6	6
Tail pinch response Normal		6	6	6	6
Pupillary reflex Pass, both		6	6	6	6
Aerial righting reflex (Total score: Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		89±23	81±16	60±16	64±14

No significant difference between treated group and control group.

Table 2-21 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Grip strength (Week 4)

Sex	Dose mg/kg		Fore limb g	Hind limb g
Male	0	No.	12	12
		Mean	1062	494
		S.D.	169	77
	100	No.	6	6
		Mean	951	435
		S.D.	158	94
	300	No.	6	6
		Mean	992	494
		S.D.	62	79
	1000	No.	12	12
		Mean	978	456
		S.D.	108	85
Female	0	No.	12	12
		Mean	871	453
		S.D.	100	87
	100	No.	6	6
		Mean	830	453
		S.D.	123	46
	300	No.	6	6
		Mean	779	356
		S.D.	148	100
	1000	No.	12	12
		Mean	796	371
		S.D.	176	127

No significant difference in any treated groups from control group.

Table 2-22 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Grip strength (Week 2 of recovery)

Sex	Dose mg/kg		Fore limb g	Hind limb g
Male	0	No.	6	6
		Mean	1262	546
		S.D.	111	96
	1000	No.	6	6
		Mean	1092	571
		S.D.	235	86
Female	0	No.	6	6
		Mean	1074	560
		S.D.	126	112
	1000	No.	6	6
		Mean	903	408*
		S.D.	143	28AT

* : $p<0.05$ (Significant difference from control group)
AT : Aspin-Welch t-test

Table 2-23 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Motor activity (Week 4)

Sex	Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
Male	0	No.	12	12	12	12	12	12	12
		Mean	407	382	319	339	289	256	1992
		S.D.	31	62	61	75	124	147	334
	100	No.	6	6	6	6	6	6	6
		Mean	427	390	327	341	317	250	2051
		S.D.	44	54	68	45	64	142	273
	300	No.	6	6	6	6	6	6	6
		Mean	422	385	387	312	275	175	1956
		S.D.	48	73	67	42	124	168	309
	1000	No.	12	12	12	12	12	12	12
		Mean	388	327	163**	126**	101**	49**	1154**
		S.D.	45	71	147D	141DT	118D	89D	408D
Female	0	No.	12	12	12	12	12	12	12
		Mean	418	355	320	234	249	247	1823
		S.D.	38	52	84	103	140	154	387
	100	No.	6	6	6	6	6	6	6
		Mean	413	318	273	276	137	114	1531
		S.D.	37	87	57	97	90	103	249
	300	No.	6	6	6	6	6	6	6
		Mean	401	340	229	238	154	121	1483
		S.D.	25	104	148	180	134	124	512
	1000	No.	12	12	12	12	12	12	12
		Mean	383	263	105**	72**	24**	20**	867**
		S.D.	59	125	98D	121D	42DT	40DT	265D

** : $p<0.01$ (Significant difference from control group)
D : Dunnett's test
DT : Dunnett-type rank test

Table 2-24 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Motor activity (Week 2 of recovery)

Sex	Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
Male	0	No.	6	6	6	6	6	6	6
		Mean	397	349	315	227	218	221	1726
		S.D.	31	58	63	74	73	111	265
	1000	No.	6	6	6	6	6	6	6
		Mean	408	372	280	276	274	208	1819
		S.D.	27	46	63	51	139	125	256
Female	0	No.	6	6	6	6	6	6	6
		Mean	392	277	197	241	242	225	1573
		S.D.	19	74	150	147	206	122	528
	1000	No.	6	6	6	6	6	6	6
		Mean	378	292	247	286	258	209	1670
		S.D.	39	58	140	79	125	132	288

No significant difference between treated group and control group.

Table 3-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Body weight (Administration period)

Sex	Dose mg/kg		Day of administration 1	4	7	10	14	17	21	24	28	Gain 1-28
	0	No.	12	12	12	12	12	12	12	12	12	12
		Mean	210	236	264	289	322	343	365	380	398	188
		S.D.	7	9	10	12	16	18	23	25	28	26
Male	100	No.	6	6	6	6	6	6	6	6	6	6
		Mean	210	235	264	291	322	345	367	380	401	191
		S.D.	7	8	9	8	6	8	5	10	10	7
	300	No.	6	6	6	6	6	6	6	6	6	6
		Mean	209	235	261	285	317	339	364	377	398	189
		S.D.	9	14	19	23	31	34	39	39	46	38
	1000	No.	12	12	12	12	12	12	12	12	12	12
		Mean	209	232	260	286	314	337	358	369	387	178
		S.D.	9	10	12	15	17	20	24	28	29	23
	0	No.	12	12	12	12	12	12	12	12	12	12
		Mean	158	168	181	190	206	218	229	236	248	90
		S.D.	7	11	13	16	19	19	22	25	27	22
Female	100	No.	6	6	6	6	6	6	6	6	6	6
		Mean	157	168	177	187	201	209	221	228	241	84
		S.D.	7	8	9	14	20	20	22	23	31	28
	300	No.	6	6	6	6	6	6	6	6	6	6
		Mean	159	172	182	192	204	215	223	227	238	79
		S.D.	6	9	11	10	13	15	17	18	18	16
	1000	No.	12	12	12	12	12	12	12	12	12	12
		Mean	157	168	180	191	203	210	222	229	239	82
		S.D.	4	5	7	8	11	11	12	12	13	12

Unit : g
No significant difference in any treated groups from control group.

Table 3-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Body weight (Recovery period)

Sex	Dose mg/kg		Day of recovery 1	3	7	10	14	Gain 1-14
Male	0	No.	6	6	6	6	6	6
		Mean	404	416	436	448	463	60
		S.D.	35	39	42	44	50	16
	1000	No.	6	6	6	6	6	6
		Mean	394	405	424	434	452	58
		S.D.	38	37	41	41	46	11
Female	0	No.	6	6	6	6	6	6
		Mean	253	261	269	271	273	21
		S.D.	27	30	33	33	38	11
	1000	No.	6	6	6	6	6	6
		Mean	231	237	249	254	259	28
		S.D.	16	15	18	18	14	7

Unit : g
No significant difference between treated group and control group.

Table 4-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Food consumption (Administration period)

Sex	Dose mg/kg		Day of administration 1	4	7	10	14	17	21	24	28
	0	No.	12	12	12	12	12	12	12	12	12
		Mean	24	23	26	25	27	26	26	24	25
		S.D.	2	2	2	2	2	2	2	2	2
Male	100	No.	6	6	6	6	6	6	6	6	6
		Mean	24	23	25	25	26	25	25	24	25
		S.D.	1	1	2	2	1	1	1	1	1
	300	No.	6	6	6	6	6	6	6	6	6
		Mean	23	23	25	24	26	26	26	24	25
		S.D.	2	3	4	4	5	5	4	4	5
	1000	No.	12	12	12	12	12	12	12	12	12
		Mean	24	22	25	24	26	26	25	24	24
		S.D.	2	2	2	2	2	2	2	3	2
	0	No.	12	12	12	12	12	12	12	12	12
		Mean	19	17	17	17	18	18	18	17	19
		S.D.	2	2	1	1	2	1	2	2	2
Female	100	No.	6	6	6	6	6	6	6	6	6
		Mean	18	16	17	16	17	17	18	16	18
		S.D.	3	2	1	3	3	2	2	3	2
	300	No.	6	6	6	6	6	6	6	6	6
		Mean	20	17	18	17	18	17	17	16	18
		S.D.	2	2	2	1	2	2	2	2	2
	1000	No.	12	12	12	12	12	12	12	12	12
		Mean	18	16	17	17	18	17	18	17	18
		S.D.	1	2	1	2	1	2	2	1	2

Unit : g/rat/day
No significant difference in any treated groups from control group.

Table 4-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Food consumption (Recovery period)

Sex	Dose mg/kg		Day of recovery 3	7	10	14
Male	0	No.	6	6	6	6
		Mean	30	31	31	30
		S.D.	3	3	3	2
	1000	No.	6	6	6	6
		Mean	27	29	29	29
		S.D.	2	2	2	3
Female	0	No.	6	6	6	6
		Mean	22	22	21	20
		S.D.	2	3	2	3
	1000	No.	6	6	6	6
		Mean	21	21	20	20
		S.D.	2	2	2	1

Unit : g/rat/day
No significant difference between treated group and control group.

Table 5-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Urinalysis (Week 4)

Sex	Dose mg/kg	No.	pH									1) Protein						2) Ketone body						3) Glucose					
			5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++
Male	0	12	0	0	0	1	2	1	3	3	2	0	3	8	1	0	0	1	4	7	0	0	0	12	0	0	0	0	0
	100	6	0	0	0	0	0	1	1	3	1	0	3	2	1	0	0	3	1	2	0	0	0	6	0	0	0	0	0
	300	6	0	0	0	4	0	0	1	1	0	0	0	6	0	0	0	0	2	3	1	0	0	6	0	0	0	0	0
	1000	12	0	0	0	0	2	0	4	6	0	0	2	9	1	0	0	2	3	7	0	0	0	12	0	0	0	0	0
Female	0	12	0	0	0	3	3	3	3	0	0	5	3	4	0	0	0	4	4	4	0	0	0	12	0	0	0	0	0
	100	6	0	0	0	2	1	1	1	1	0	0	2	4	0	0	0	0	3	3	0	0	0	6	0	0	0	0	0
	300	6	0	0	2	3	0	0	1	0	0	0	2	4	0	0	0	0	1	5	0	0	0	6	0	0	0	0	0
	1000	12	0	0	1	6	1	3	1	0	0	0	2	8	2	0	0	0	4	8	0	0	0	12	0	0	0	0	0

1) - : <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL

2) - : <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL

3) - : <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL

Table 5-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Urinalysis (Week 4)

Sex	Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color		
			-	+-	+	++	+++	-	+	++	+++	++++	+-	+	++	+++	++++	LY	Y	DY
	0	12	12	0	0	0	0	12	0	0	0	0	10	2	0	0	0	0	12	0
Male	100	6	6	0	0	0	0	6	0	0	0	0	5	1	0	0	0	0	6	0
	300	6	6	0	0	0	0	6	0	0	0	0	4	2	0	0	0	0	6	0
	1000	12	12	0	0	0	0	12	0	0	0	0	8	4	0	0	0	0	12	0
	0	12	12	0	0	0	0	12	0	0	0	0	10	2	0	0	0	0	12	0
Female	100	6	6	0	0	0	0	6	0	0	0	0	6	0	0	0	0	0	6	0
	300	6	6	0	0	0	0	6	0	0	0	0	5	1	0	0	0	0	6	0
	1000	12	12	0	0	0	0	12	0	0	0	0	5	7	0	0	0	0	12	0

4) - : <0.03 mg/dL +- : 0.03 - 0.05 mg/dL + : 0.06 - 0.15 mg/dL ++ : 0.16 - 0.75 mg/dL +++ : >0.75 mg/dL
5) - : <0.5 mg/dL + : 0.5 - 1.5 mg/dL ++ : 1.6 - 5.0 mg/dL +++ : 5.1 - 10.0 mg/dL ++++ : >10.0 mg/dL
6) +- : <2.0 mg/dL + : 2.0 - 3.5 mg/dL ++ : 3.6 - 7.0 mg/dL +++ : 7.1 - 12.0 mg/dL ++++ : >12.0 mg/dL
7) LY : Light yellow Y : Yellow DY : Dark yellow

Table 5-3 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Urinalysis (Week 4)

Sex	Dose mg/kg	No.	URINE SEDIMENT																																	
			RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS						CRYSTALLIZATION CO				
			-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
Male	0	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	12	0	0	0	0	12	0	0	0	0
	100	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	6	0	0	0	0	6	0	0	0	0
	300	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	6	0	0	0	0	5	1	0	0	0
	1000	12	12	0	0	0	0	12	0	0	0	0	0	11	1	0	0	11	1	0	0	0	12	0	0	12	0	0	0	0	11	1	0	0	0
Female	0	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	12	0	0	0	0	12	0	0	0	0
	100	6	6	0	0	0	0	5	1	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	6	0	0	0	0	5	1	0	0	0
	300	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	6	0	0	0	0	6	0	0	0	0
	1000	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	11	1	0	0	0	10	2	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-4 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Water intake and urinalysis (Week 4)

Sex	Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
	0	12	Mean	30	6.5	2136
			S.D.	5	3.0	382
Male	100	6	Mean	37	9.1	1734
			S.D.	5	3.0	354
	300	6	Mean	31	7.6	2068
			S.D.	5	1.4	285
	1000	12	Mean	38*	8.3	2082
			S.D.	9D	3.4	490
	0	12	Mean	28	5.4	2183
			S.D.	7	4.3	648
Female	100	6	Mean	30	6.0	2027
			S.D.	11	2.8	493
	300	6	Mean	29	5.3	2241
			S.D.	9	4.2	686
	1000	12	Mean	32	4.8	2325
			S.D.	7	2.1	445

* : $p<0.05$ (Significant difference from control group)
D : Dunnett's test

Table 5-5 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Urinalysis (Week 2 of recovery)

Sex	Dose mg/kg	No.	pH									1) Protein						2) Ketone body						3) Glucose					
			5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++
Male	0	6	0	0	0	0	0	0	1	4	1	0	4	2	0	0	0	1	2	3	0	0	0	6	0	0	0	0	0
	1000	6	0	0	0	0	0	0	0	3	3	1	3	2	0	0	0	3	0	3	0	0	0	6	0	0	0	0	0
Female	0	6	0	0	0	0	2	2	0	1	1	3	0	3	0	0	0	3	0	3	0	0	0	6	0	0	0	0	0
	1000	6	0	0	0	2	0	1	0	3	0	2	3	1	0	0	0	1	2	3	0	0	0	6	0	0	0	0	0

1) - : <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL
2) - : <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL
3) - : <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL

Table 5-6 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Urinalysis (Week 2 of recovery)

Sex	Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color		
			-	+-	+	++	+++	-	+	++	+++	++++	+-	+	++	+++	++++	LY	Y	DY
Male	0	6	5	1	0	0	0	6	0	0	0	0	6	0	0	0	0	0	6	0
	1000	6	5	1	0	0	0	6	0	0	0	0	6	0	0	0	0	0	6	0
Female	0	6	6	0	0	0	0	5	1	0	0	0	5	1	0	0	0	0	6	0
	1000	6	5	1	0	0	0	6	0	0	0	0	6	0	0	0	0	0	6	0

4) - : <0.03 mg/dL +- : 0.03 - 0.05 mg/dL + : 0.06 - 0.15 mg/dL ++ : 0.16 - 0.75 mg/dL +++ : >0.75 mg/dL
5) - : <0.5 mg/dL + : 0.5 - 1.5 mg/dL ++ : 1.6 - 5.0 mg/dL +++ : 5.1 - 10.0 mg/dL ++++ : >10.0 mg/dL
6) +- : <2.0 mg/dL + : 2.0 - 3.5 mg/dL ++ : 3.6 - 7.0 mg/dL +++ : 7.1 - 12.0 mg/dL ++++ : >12.0 mg/dL
7) LY : Light yellow Y : Yellow DY : Dark yellow

Table 5-7 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Urinalysis (Week 2 of recovery)

Sex	Dose mg/kg	No.	URINE SEDIMENT																													
			RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
			-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
Male	0	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	4	2	0	0	0	6	0	0	0	0
	1000	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	5	1	0	0	0	6	0	0	0	0
Female	0	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	5	1	0	0	0	6	0	0	0	0
	1000	6	6	0	0	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0	6	0	0	5	1	0	0	0	6	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-8 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Water intake and urinalysis (Week 2 of recovery)

Sex	Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
Male	0	6	Mean	35	15.2	2000
			S.D.	5	4.4	230
	1000	6	Mean	38	12.9	1716
			S.D.	6	4.6	291
Female	0	6	Mean	32	9.0	2122
			S.D.	8	3.9	542
	1000	6	Mean	29	7.8	2064
			S.D.	4	3.5	557

No significant difference between treated group and control group.

Table 6-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Hematology (Day 28)

Sex	Dose mg/kg	No.		RBC $X10^4/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Reticul. %	PLT $X10^4/\mu L$	PT s	APTT s	FIB mg/dL
	0	6	Mean	790	16.1	42.6	54.0	20.4	37.8	2.1	134.1	13.9	21.9	358
			S.D.	37	0.6	1.0	1.9	0.7	0.5	0.5	31.2	1.4	4.1	30
Male	100	6	Mean	799	16.4	43.0	53.8	20.5	38.1	2.2	120.8	13.7	20.5	370
			S.D.	40	0.6	1.8	1.1	0.5	0.5	0.4	11.0	0.5	3.0	26
	300	6	Mean	807	16.5	43.8	54.2	20.5	37.7	2.3	115.3	15.6	21.7	349
			S.D.	22	0.4	1.3	1.9	0.6	0.4	0.4	12.1	2.3	2.8	25
	1000	6	Mean	802	16.6	44.1	55.1	20.7	37.6	2.2	111.9	15.7	24.7	359
			S.D.	35	0.5	1.1	1.3	0.4	0.2	0.3	9.3	2.7	2.4	22
	0	6	Mean	769	15.8	40.9	53.2	20.6	38.8	2.0	130.5	12.5	16.0	272
			S.D.	43	0.6	1.2	1.5	0.5	0.4	0.5	9.6	0.7	1.8	17
Female	100	6	Mean	801	16.4	42.7	53.4	20.5	38.3	1.9	137.5	12.4	17.8	268
			S.D.	41	0.8	2.2	1.9	0.6	0.3	0.5	18.2	0.7	2.4	26
	300	6	Mean	805	16.6	43.3	53.9	20.6	38.3	1.5	127.0	12.3	18.0	267
			S.D.	25	0.7	1.6	0.8	0.3	0.3	0.3	11.8	0.6	2.0	29
	1000	6	Mean	812	16.2	42.2	51.9	19.9	38.4	1.7	136.1	12.5	18.1	277
			S.D.	25	0.7	1.5	1.6	0.7	0.3	0.3	12.3	0.4	2.0	20

No significant difference in any treated groups from control group.

Table 6-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Hematology (Day 28)

Sex	Dose mg/kg	No.		WBC	Differential leukocyte counts (%)					
				X10²/μL	LYM	NE	EOSINO	BASO	MONO	LUC
	0	6	Mean	95.2	76.6	19.2	1.3	0.4	1.9	0.7
			S.D.	19.3	5.8	4.9	0.5	0.1	0.5	0.3
Male	100	6	Mean	76.7	76.8	19.2	0.9	0.4	2.1	0.7
			S.D.	15.8	8.4	7.6	0.4	0.1	1.0	0.2
	300	6	Mean	114.1	77.8	18.3	1.0	0.5	1.9	0.6
			S.D.	30.3	4.1	3.6	0.3	0.1	0.5	0.1
	1000	6	Mean	82.6	75.2	20.3	1.0	0.5	2.1	0.9
			S.D.	25.8	10.1	10.0	0.3	0.2	0.5	0.1
	0	6	Mean	69.6	76.2	19.1	1.1	0.3	2.5	0.7
			S.D.	20.5	8.1	6.7	0.5	0.1	1.6	0.4
Female	100	6	Mean	71.5	77.2	18.8	1.3	0.4	1.6	0.8
			S.D.	11.9	9.5	9.0	0.5	0.2	0.4	0.2
	300	6	Mean	77.2	81.0	14.7	1.3	0.5	1.8	0.8
			S.D.	26.4	6.2	6.0	0.3	0.1	0.7	0.2
	1000	6	Mean	85.7	77.5	18.6	0.9	0.4	1.6	1.0
			S.D.	22.0	5.4	5.6	0.4	0.1	0.5	0.2

LUC : Large unstained cells
No significant difference in any treated groups from control group.

Table 6-3 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Hematology (Week 2 of recovery)

Sex	Dose mg/kg	No.		RBC $\times 10^4/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Reticul. %	PLT $\times 10^4/\mu L$	PT s	APTT s	FIB mg/dL
Male	0	6	Mean	836	16.5	42.6	51.0	19.8	38.8	2.0	117.3	13.9	20.2	373
			S.D.	40	0.6	1.4	2.2	0.8	0.3	0.4	8.0	1.2	2.0	29
	1000	6	Mean	862	17.1	43.7	50.8	19.8	39.0	1.8	118.1	14.4	21.8	381
			S.D.	15	0.4	1.2	0.7	0.2	0.3	0.3	9.9	1.4	3.6	31
Female	0	6	Mean	807	16.1	41.2	51.1	20.0	39.2	1.8	130.1	11.8	15.6	276
			S.D.	36	0.6	1.7	2.7	0.8	0.6	0.3	7.6	0.5	2.4	20
	1000	6	Mean	850*	16.6	42.3	49.8	19.6	39.2	1.4	137.0	12.2	17.3	281
			S.D.	23T	0.3	0.6	1.3	0.5	0.3	0.2	9.1	0.7	3.1	22

* : $p<0.05$ (Significant difference from control group)
T : Student's t-test

Table 6-4 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Hematology (Week 2 of recovery)

Sex	Dose mg/kg	No.		WBC	Differential leukocyte counts (%)					
				X10²/μL	LYM	NE	EOSINO	BASO	MONO	LUC
Male	0	6	Mean	105.8	73.5	21.8	1.5	0.4	2.3	0.6
			S.D.	31.4	5.9	6.0	0.2	0.1	0.6	0.2
	1000	6	Mean	98.1	78.7	16.6	1.1	0.5	2.4	0.7
			S.D.	36.1	4.8	4.5	0.4	0.2	0.5	0.3
Female	0	6	Mean	68.3	79.9	15.8	1.0	0.3	2.1	0.9
			S.D.	12.4	6.6	6.0	0.3	0.1	1.2	0.2
	1000	6	Mean	81.2	75.7	19.3	1.4	0.4	2.1	1.2
			S.D.	22.4	5.1	6.0	0.5	0.1	0.7	0.5

LUC : Large unstained cells
No significant difference between treated group and control group.

Table 7-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Blood chemistry (Day 28)

Sex	Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	γ-GTP IU/L	ALP IU/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
Male	0	6	Mean	59	27	53	1	774	51	31	91	0.1	135
			S.D.	6	2	9	0	60	11	9	13	0.1	17
	100	6	Mean	56	27	51	1	631	59	38	103	0.1	141
			S.D.	3	5	8	0	114	9	19	10	0.1	4
	300	6	Mean	59	27	51	1	628	49	36	92	0.0	139
			S.D.	5	2	7	0	156	9	18	13	0.1	10
	1000	6	Mean	58	27	65	1	604*	59	31	100	0.1	140
			S.D.	5	2	19	1	97D	10	10	9	0.1	15
Female	0	6	Mean	65	27	68	2	452	51	9	93	0.1	112
			S.D.	9	10	17	1	93	10	2	14	0.0	12
	100	6	Mean	58	22	60	1	428	51	8	98	0.1	122
			S.D.	5	2	13	0	107	17	4	28	0.1	13
	300	6	Mean	58	24	53	1	366	56	10	101	0.1	119
			S.D.	6	3	10	0	55	21	4	27	0.1	16
	1000	6	Mean	55	25	59	1	405	63	12	112	0.1	124
			S.D.	6	2	9	1	74	13	6	24	0.1	14

* : $p<0.05$ (Significant difference from control group)
D : Dunnett's test

Table 7-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Blood chemistry (Day 28)

Sex	Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
	0	6	Mean	11	0.23	142	4.9	107	9.8	8.0	5.9	2.9	0.93
			S.D.	2	0.03	1	0.3	1	0.3	0.8	0.2	0.1	0.02
Male	100	6	Mean	11	0.21	142	5.2	108	10.0	7.9	6.0	2.8	0.91
			S.D.	1	0.01	2	0.3	1	0.3	0.6	0.3	0.1	0.04
	300	6	Mean	12	0.23	142	5.0	107	9.9	8.0	5.7	2.8	0.93
			S.D.	1	0.03	1	0.3	2	0.3	0.4	0.2	0.1	0.05
	1000	6	Mean	11	0.22	142	5.0	107	10.0	7.9	6.1	2.9	0.93
			S.D.	1	0.01	1	0.3	1	0.2	0.5	0.2	0.1	0.07
	0	6	Mean	15	0.27	142	4.5	109	9.9	7.4	6.1	3.0	0.98
			S.D.	2	0.03	1	0.1	1	0.3	0.6	0.2	0.1	0.04
Female	100	6	Mean	14	0.25	142	4.7	110	9.9	7.3	5.9	3.0	1.01
			S.D.	2	0.03	1	0.4	1	0.3	0.4	0.2	0.1	0.03
	300	6	Mean	16	0.29	141	4.5	109	10.0	7.9	6.0	3.0	1.00
			S.D.	1	0.02	1	0.2	2	0.3	0.6	0.2	0.1	0.06
	1000	6	Mean	15	0.26	142	4.5	108	10.1	7.9	6.3	3.1	0.97
			S.D.	2	0.03	2	0.3	1	0.2	0.3	0.3	0.1	0.07

No significant difference in any treated groups from control group.

Table 7-3 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Blood chemistry (Week 2 of recovery)

Sex	Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	γ-GTP IU/L	ALP IU/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
Male	0	6	Mean	60	28	59	1	576	56	50	99	0.1	149
			S.D.	5	5	16	0	156	8	16	9	0.0	20
	1000	6	Mean	60	32	59	1	486	62	51	107	0.1	151
			S.D.	7	6	10	1	42	12	11	16	0.0	21
Female	0	6	Mean	60	24	45	1	274	68	17	122	0.1	117
			S.D.	8	3	9	0	47	13	9	22	0.0	20
	1000	6	Mean	62	24	49	1	383	66	17	119	0.1	115
			S.D.	7	1	15	1	128	11	4	15	0.0	11

No significant difference between treated group and control group.

Table 7-4 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Blood chemistry (Week 2 of recovery)

Sex	Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
Male	0	6	Mean	15	0.24	144	4.6	107	9.9	7.3	6.1	2.8	0.84
			S.D.	1	0.03	2	0.3	1	0.3	0.5	0.1	0.1	0.05
	1000	6	Mean	14	0.24	143	4.5	107	9.7	7.4	6.0	2.8	0.88
			S.D.	2	0.02	3	0.3	3	0.3	0.5	0.3	0.1	0.03
Female	0	6	Mean	16	0.30	143	4.5	109	10.1	7.3	6.4	3.1	0.94
			S.D.	1	0.04	1	0.2	1	0.2	0.5	0.2	0.1	0.08
	1000	6	Mean	15	0.28	144	4.6	110	10.0	7.2	6.3	3.0	0.92
			S.D.	2	0.02	1	0.3	1	0.3	0.3	0.4	0.2	0.04

No significant difference between treated group and control group.

Table 8-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Day 28)

Male

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
	0	No.	6	6	6	6	6	6	6	6
		Mean	374	2.05	431	1.21	11.68	0.62	2.88	59
		S.D.	24	0.05	130	0.06	1.34	0.05	0.25	8
Absolute	100	No.	6	6	6	6	6	6	6	6
		Mean	376	2.01	478	1.25	12.40	0.66	2.86	55
		S.D.	11	0.09	76	0.07	1.09	0.09	0.14	6
	300	No.	6	6	6	6	6	6	6	6
		Mean	370	2.00	559	1.25	11.71	0.71	2.83	61
		S.D.	40	0.09	92	0.18	2.70	0.13	0.45	13
	1000	No.	6	6	6	6	6	6	6	6
		Mean	360	1.99	447	1.18	11.77	0.60	2.83	62
		S.D.	26	0.07	71	0.08	0.89	0.12	0.26	11
	0	No.		6	6	6	6	6	6	6
		Mean		0.55	115	0.33	3.12	0.16	0.77	16
		S.D.		0.03	35	0.04	0.19	0.01	0.05	2
Relative	100	No.		6	6	6	6	6	6	6
		Mean		0.54	127	0.33	3.30	0.18	0.76	15
		S.D.		0.03	19	0.02	0.30	0.02	0.04	2
	300	No.		6	6	6	6	6	6	6
		Mean		0.54	152	0.34	3.13	0.19*	0.76	16
		S.D.		0.04	26	0.03	0.38	0.02D	0.06	3
	1000	No.		6	6	6	6	6	6	6
		Mean		0.55	125	0.33	3.27	0.17	0.79	17
		S.D.		0.03	21	0.03	0.13	0.03	0.04	2

* : $p<0.05$ (Significant difference from control group)
D : Dunnett's test

Table 8-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Day 28)

Male

	Dose mg/kg		Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
	0	No.	6	6
		Mean	3.21	862
		S.D.	0.18	49
Absolute	100	No.	6	6
		Mean	3.18	863
		S.D.	0.27	94
	300	No.	6	6
		Mean	3.05	844
		S.D.	0.52	66
	1000	No.	6	6
		Mean	3.01	836
		S.D.	0.32	96
	0	No.	6	6
		Mean	0.86	232
		S.D.	0.05	26
Relative	100	No.	6	6
		Mean	0.85	230
		S.D.	0.07	23
	300	No.	6	6
		Mean	0.82	229
		S.D.	0.08	16
	1000	No.	6	6
		Mean	0.84	233
		S.D.	0.09	30

No significant difference in any treated groups from control group.

Table 8-3 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Day 28)

Female

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
	0	No.	6	6	6	6	6	6	6	6
		Mean	231	1.92	484	0.83	6.90	0.50	1.78	69
		S.D.	24	0.06	190	0.10	1.01	0.09	0.16	11
Absolute	100	No.	6	6	6	6	6	6	6	6
		Mean	224	1.91	444	0.82	6.68	0.53	1.74	67
		S.D.	25	0.09	181	0.10	1.10	0.14	0.19	9
	300	No.	6	6	6	6	6	6	6	6
		Mean	219	1.88	437	0.77	6.63	0.48	1.58	68
		S.D.	15	0.06	103	0.09	0.95	0.11	0.14	7
	1000	No.	6	6	6	6	6	6	6	6
		Mean	228	1.89	470	0.84	7.62	0.55	1.76	72
		S.D.	8	0.07	145	0.06	0.28	0.09	0.12	5
	0	No.		6	6	6	6	6	6	6
		Mean		0.84	206	0.36	2.97	0.22	0.77	30
		S.D.		0.08	62	0.01	0.16	0.03	0.03	5
Relative	100	No.		6	6	6	6	6	6	6
		Mean		0.86	194	0.37	2.98	0.24	0.78	30
		S.D.		0.07	53	0.02	0.25	0.04	0.05	4
	300	No.		6	6	6	6	6	6	6
		Mean		0.86	200	0.35	3.02	0.22	0.72	31
		S.D.		0.04	46	0.02	0.24	0.04	0.04	1
	1000	No.		6	6	6	6	6	6	6
		Mean		0.83	206	0.37	3.35*	0.24	0.77	32
		S.D.		0.02	59	0.02	0.13D	0.04	0.05	3

* : $p<0.05$ (Significant difference from control group)
D : Dunnett's test

Table 8-4 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Day 28)

Female

	Dose mg/kg		Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	6	6
		Mean	91.7	432
		S.D.	14.6	112
	100	No.	6	6
		Mean	89.3	487
		S.D.	15.6	195
	300	No.	6	6
		Mean	74.9	419
		S.D.	5.9	156
	1000	No.	6	6
		Mean	92.7	438
		S.D.	14.3	95
Relative	0	No.	6	6
		Mean	39.8	186
		S.D.	6.4	40
	100	No.	6	6
		Mean	39.9	213
		S.D.	4.3	62
	300	No.	6	6
		Mean	34.4	189
		S.D.	3.2	60
	1000	No.	6	6
		Mean	40.7	192
		S.D.	6.1	41

No significant difference in any treated groups from control group.

Table 8-5 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Week 2 of recovery)

Male

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	0	No.	6	6	6	6	6	6	6	6
		Mean	435	2.06	432	1.32	12.77	0.75	3.05	59
		S.D.	46	0.08	126	0.17	2.11	0.16	0.25	9
	1000	No.	6	6	6	6	6	6	6	6
		Mean	421	2.12	495	1.29	12.29	0.72	2.93	65
		S.D.	43	0.07	110	0.17	2.26	0.12	0.33	13
Relative	0	No.		6	6	6	6	6	6	6
		Mean		0.48	99	0.30	2.92	0.17	0.71	14
		S.D.		0.04	27	0.02	0.19	0.03	0.06	2
	1000	No.		6	6	6	6	6	6	6
		Mean		0.51	118	0.31	2.90	0.17	0.70	15
		S.D.		0.04	25	0.06	0.23	0.02	0.05	2

No significant difference between treated group and control group.

Table 8-6 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Week 2 of recovery)

Male

	Dose mg/kg		Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	0	No.	6	6
		Mean	3.20	1054
		S.D.	0.27	93
	1000	No.	6	6
		Mean	3.23	1063
		S.D.	0.25	58
Relative	0	No.	6	6
		Mean	0.74	246
		S.D.	0.11	46
	1000	No.	6	6
		Mean	0.77	254
		S.D.	0.08	23

No significant difference between treated group and control group.

Table 8-7 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Week 2 of recovery)

Female

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	0	No.	6	6	6	6	6	6	6	6
		Mean	258	1.96	374	0.84	6.96	0.56	1.79	67
		S.D.	33	0.05	61	0.07	1.00	0.08	0.15	15
	1000	No.	6	6	6	6	6	6	6	6
		Mean	242	1.94	353	0.84	6.67	0.45*	1.83	69
		S.D.	16	0.07	82	0.07	0.57	0.06T	0.14	14
Relative	0	No.		6	6	6	6	6	6	6
		Mean		0.77	147	0.33	2.70	0.22	0.70	26
		S.D.		0.09	26	0.02	0.07	0.02	0.05	5
	1000	No.		6	6	6	6	6	6	6
		Mean		0.81	146	0.35	2.76	0.19*	0.76	29
		S.D.		0.07	30	0.02	0.09	0.02T	0.05	5

* : $p<0.05$ (Significant difference from control group)
T : Student's t-test

Table 8-8 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Absolute and relative organ weight (Week 2 of recovery)

Female

	Dose mg/kg		Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	6	6
		Mean	85.3	476
		S.D.	8.8	155
	1000	No.	6	6
		Mean	76.6	418
		S.D.	15.4	106
Relative	0	No.	6	6
		Mean	33.4	186
		S.D.	4.1	59
	1000	No.	6	6
		Mean	31.6	173
		S.D.	5.1	45

No significant difference between treated group and control group.

Table 9-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Gross pathological findings (Day 28)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	100	300	1000	0	100	300	1000
	Number:	6	6	6	6	6	6	6	6
Kidney									
Focus,depressed		0	0	0	0	0	0	1	0
Cyst		0	0	0	1	0	0	0	0
Lung(bronchus)									
Focus,dark red		0	0	1	1	0	0	0	0
Uterus									
Cyst		-	-	-	-	0	1	0	0

- : Not applicable

Table 9-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Gross pathological findings (Week 2 of recovery)

Organs	Sex:	M	M	F	F
	Dose(mg/kg):	0	1000	0	1000
Findings	Number:	6	6	6	6
All tissues					
Not remarkable		6	6	6	6

Table 10-1 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Histopathological findings (Day 28)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	100	300	1000	0	100	300	1000
	Number:	6	6	6	6	6	6	6	6
Adrenal									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Bone+Bone marrow,femoral									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Bone+Bone marrow,sternal									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Cerebellum									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Cerebrum									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Epididymis									
Number examined		6	0	0	6	-	-	-	-
Not remarkable		6	0	0	6	-	-	-	-
Eye									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Heart									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		5	0	0	6	6	0	0	6
Cardiomyopathy		1	0	0	0	0	0	0	0
minimal		1	0	0	0	0	0	0	0
Intestine,duodenum									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Intestine,jejunum									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Intestine,ileum(Peyer's patch)									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Intestine,cecum									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		5	0	0	6	6	0	0	6
Cell infiltration,mucosal		1	0	0	0	0	0	0	0
minimal		1	0	0	0	0	0	0	0
Intestine,colon									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Intestine,rectum									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Kidney									
Number examined		6	0	0	6	6	0	1	6
Not remarkable		5	0	0	3	6	0	0	5

- : Not applicable

Table 10-2 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Histopathological findings (Day 28)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	100	300	1000	0	100	300	1000
	Number:	6	6	6	6	6	6	6	6
Kidney (continued)									
Cyst		0	0	0	1	0	0	0	0
minimal		0	0	0	1	0	0	0	0
Regeneration,tubular		1	0	0	2	0	0	1	1
minimal		1	0	0	2	0	0	0	1
mild		0	0	0	0	0	0	1	0
Eosinophilic body,tubular cell		1	0	0	2	0	0	0	0
minimal		1	0	0	2	0	0	0	0
Liver									
Number examined		6	6	6	6	6	6	6	6
Not remarkable		0	1	3	0	0	1	1	1
Vacuolation,hepatocyte,periportal		6	4	2	1	5	3	4	4
minimal		5	4	2	1	3	3	3	3
mild		1	0	0	0	2	0	1	1
Microgranuloma		1	1	0	2	4	4	4	4
minimal		1	1	0	2	3	4	4	4
mild		0	0	0	0	1	0	0	0
Hypertrophy,hepatocytic,central		0	0	1	5	0	0	0	3
minimal		0	0	1	2	0	0	0	3
mild		0	0	0	3	0	0	0	0
Lung(bronchus)									
Number examined		6	0	1	6	6	0	0	6
Not remarkable		6	0	0	4	6	0	0	6
Hemorrhage,focal		0	0	1	1	0	0	0	0
mild		0	0	1	1	0	0	0	0
Accumulation,foamy cell		0	0	0	1	0	0	0	0
minimal		0	0	0	1	0	0	0	0
Lymph node,mesenteric									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Lymph node,submandibular									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Ovary									
Number examined		-	-	-	-	6	0	0	6
Not remarkable		-	-	-	-	6	0	0	6
Parathyroid									
Number examined		5	0	0	6	6	0	0	5
Not remarkable		5	0	0	6	6	0	0	5
No sample		1	0	0	0	0	0	0	1
Pituitary									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		5	0	0	6	6	0	0	6
Cyst		1	0	0	0	0	0	0	0
minimal		1	0	0	0	0	0	0	0
Prostate									
Number examined		6	0	0	6	-	-	-	-
Not remarkable		2	0	0	4	-	-	-	-
Cell infiltration,interstitial		4	0	0	2	-	-	-	-
minimal		3	0	0	2	-	-	-	-
mild		1	0	0	0	-	-	-	-
Sciatic nerve									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6

- : Not applicable

Table 10-3 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Histopathological findings (Day 28)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	100	300	1000	0	100	300	1000
	Number:	6	6	6	6	6	6	6	6
Skeletal muscle,femoral									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Spinal cord,thoracic									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Spleen									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		2	0	0	3	5	0	0	6
Hematopoiesis,extramedullary		4	0	0	3	1	0	0	0
minimal		4	0	0	3	1	0	0	0
Stomach									
Number examined		6	6	6	6	6	6	6	6
Not remarkable		6	6	6	4	6	6	6	4
Erosion		0	0	0	1	0	0	0	0
minimal		0	0	0	1	0	0	0	0
Thickening,limiting ridge		0	0	0	1	0	0	0	2
minimal		0	0	0	1	0	0	0	2
Testis									
Number examined		6	0	0	6	-	-	-	-
Not remarkable		6	0	0	6	-	-	-	-
Thymus									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Thyroid									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		5	0	0	5	4	0	0	4
Ectopic thymus		1	0	0	1	0	0	0	0
minimal		1	0	0	1	0	0	0	0
Cyst,ultimobranchial		0	0	0	0	2	0	0	2
minimal		0	0	0	0	2	0	0	2
Trachea									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Urinary bladder									
Number examined		6	0	0	6	6	0	0	6
Not remarkable		6	0	0	6	6	0	0	6
Uterus									
Number examined		-	-	-	-	6	1	0	6
Not remarkable		-	-	-	-	6	0	0	6
Cyst		-	-	-	-	0	1	0	0
minimal		-	-	-	-	0	1	0	0

- : Not applicable

Table 10-4 A 28-day oral toxicity study of paracetaldehyde in rats with a recovery period of 2 weeks

Histopathological findings (Week 2 of recovery)

Organs / Findings	Sex:	M	M	F	F
	Dose(mg/kg):	0	1000	0	1000
	Number:	6	6	6	6
Liver					
Number examined		6	6	6	6
Not remarkable		2	3	3	1
Vacuolation,hepatocyte,periportal		2	1	3	2
minimal		2	1	3	2
Microgranuloma		2	2	2	5
minimal		2	2	2	5
Stomach					
Number examined		6	6	6	6
Not remarkable		6	6	6	6

要　約

2,3,4,4'-テトラヒドロキシベンゾフェノンの遺伝子突然変異誘発性の有無を検討するため，復帰突然変異試験を指標菌株として *Salmonella typhimurium* TA100，TA1535，TA98，TA1537 および *Escherichia coli* WP2*uvrA* を用い，S9 mix 非存在（直接法）および存在（代謝活性化法）下でプレインキュベーション法により行った。

用量は，用量設定試験（予備試験）の結果，菌の生育阻害が認められる用量を最高用量とし，直接法においては TA100 および TA1535 で 31.3～1000μg/プレート，TA98 および TA1537 で 1.56～50μg/プレート，WP2*uvrA* では 62.5～2000μg/プレートの範囲（公比 2），また，代謝活性化法ではいずれの菌株とも 156～5000μg/プレートの範囲（公比 2）で設定した。

試験は 2 回実施した。その結果，全ての菌株において代謝活性化の有無にかかわらず，復帰変異コロニー数の増加は認められなかった。菌の生育阻害については，直接法では TA100 の 1000μg/プレート，TA1535 の 500μg/プレート以上，TA98 および TA1537 の 25μg/プレート以上，および WP2*uvrA* の 2000μg/プレートの用量で，また，代謝活性化法では TA100，TA1535 および WP2*uvrA* の 2500μg/プレート以上，TA98 および TA1537 の 5000μg/プレートの用量で認められた。

以上の成績から，本実験条件下では，2,3,4,4'-テトラヒドロキシベンゾフェノンの細菌に対する遺伝子突然変異誘発性は陰性と判定した。

(2) 被験物質用量の増加とともに復帰変異コロニー数が増加する（用量依存性）。

(3) 2回にわたる本試験の結果から復帰変異コロニー数の増加に再現性が認められる。但し，明確な用量依存性が認められない場合においても，陽性値を示す試験結果に再現性が認められれば陽性と判定する。

結　果

試験を2回実施した結果（表2-1-1，2-1-2，2-2，3-1-1，3-1-2，3-2および図1-1，1-2，1-3，1-4，1-5，2-1，2-2，2-3，2-4，2-5），直接法および代謝活性化法のいずれの場合も，供試したすべての菌株において復帰変異コロニー数は，陰性対照値の2倍を超えることはなかった。菌の生育阻害については，直接法ではTA100の1000μg/プレート，TA1535の500μg/プレート以上，TA98およびTA1537の25μg/プレート以上，およびWP2*uvrA*の2000μg/プレートの用量で，また，代謝活性化法ではTA100，TA1535およびWP2*uvrA*の2500μg/プレート以上，TA98およびTA1537の5000μg/プレートの用量で認められた。

陰性対照群では背景データ（添付資料）の範囲内の復帰変異コロニー数が認められた。陽性対照群においては明らかな復帰変異コロニー数の増加が認められ，その程度は，それぞれ背景データ（添付資料）の範囲内の陽性値を示すものであった。また，試験に用いた菌液，溶媒，被験物質の供試液およびS9 mixなどには，雑菌の混入は認められなかった。その他，実験中被験物質の析出等，特記すべき変化は認められなかった。

結　論

2,3,4,4'-テトラヒドロキシベンゾフェノンについて遺伝子突然変異誘発性の有無を調べるため，細菌を用いる復帰突然変異試験を実施した。その結果，代謝活性化の有無にかかわらず，全ての指標菌株で復帰変異コロニー数の増加は認められなかった。

試験の有効性については，2回にわたる本試験ともに有効であることが確認された。

したがって，本実験条件下では2,3,4,4'-テトラヒドロキシベンゾフェノンの遺伝子突然変異誘発性は陰性と判定した。

表 1-1　　S9 mix 非存在下における2, 3, 4, 4'-テトラヒドロキシベンゾフェノンの用量設定試験結果〔直接法〕

用　量 〔μg/プレート〕	復帰変異コロニー数／プレート				
	塩基対置換型			フレームシフト型	
	TA100	TA1535	WP2*uvrA*	TA98	TA1537
陰性対照〔ジメチルスルホキシド〕	100	15	20	21	12
20	106	11	21	35	13
50	132	14	18	34 *	19 *
100	115	16	19	14 *	21 *
200	124	19	22	27 *	17 *
500	125	16	22	26 *	17 *
1000	136 *	4 *	23	30 *	17 *
2000	0 *	0 *	10 *	1 *	1 *
5000	0 *	0 *	0 *	0 *	0 *
陽性対照	AF−2	SA	AF−2	AF−2	9−AA
μg/プレート	0.01	0.5	0.04	0.1	80
復帰変異コロニー数／プレート	1172	439	419	285	351

＊　：菌の生育阻害が認められた。
AF-2：2-(2-フリル)-3-(5-ニトロ-2-フリル)アクリルアミド
SA　：アジ化ナトリウム
9-AA：9-アミノアクリジン

表 1-2　S9 mix 存在下における2, 3, 4, 4'-テトラヒドロキシベンゾフェノンの用量設定試験結果〔代謝活性化法〕

用量〔μg/プレート〕	復帰変異コロニー数／プレート				
	塩基対置換型			フレームシフト型	
	TA100	TA1535	WP2*uvrA*	TA98	TA1537
陰性対照〔ジメチルスルホキシド〕	110	14	28	26	18
20	138	22	20	28	22
50	117	22	13	37	15
100	129	22	19	21	19
200	129	25	20	23	11
500	137	24	23	14	15
1000	128	13	11	15	9
2000	117	8	18	18	12
5000	0 *	0 *	2 *	0 *	0 *
陽性対照	2-AA	2-AA	2-AA	2-AA	2-AA
μg/プレート	1	2	10	1	2
復帰変異コロニー数／プレート	205	108	443	280	55

＊　：菌の生育阻害が認められた。
2-AA: 2-アミノアントラセン